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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/00, 31/195		A1	(11) International Publication Number: WO 97/36579
			(43) International Publication Date: 9 October 1997 (09.10.97)
(21) International Application Number: PCT/EP97/01552		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 27 March 1997 (27.03.97)		<p>Published With international search report.</p>	
(30) Priority Data: 9606805.1 30 March 1996 (30.03.96) GB			
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(54) Title: USE OF AGONISTS OF THE PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR ALPHA FOR TREATING OBESITY			
(57) Abstract			
<p>The use of agonists of the peroxisome proliferator activated receptor alpha (PPARα) for the manufacture of a medicament for the treatment of obesity and methods of treating obesity comprising the administration of a therapeutic amount of a PPARα agonist.</p>			

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USE OF AGONISTS OF THE PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR ALPHA FOR TREATING OBESITY

The present invention is concerned with medicaments, and more particularly medicaments for use in the treatment of obesity.

5

Obesity can be described as a state of excessive accumulation of body fat, and is widely considered to be a major public health problem, being associated with substantially increased morbidity and mortality, as well as psychological problems, reduced economic achievement, and discrimination. Examples of health and social problems thought to be caused or exacerbated by obesity include coronary heart disease, stroke, obstructive sleep apnoea, diabetes mellitus, gout, hyperlipidemia, osteoarthritis, reduced fertility, impaired psychosocial function, reduced physical agility and increased risk of accidents, impaired obstetrical performance, reduced economic performance and discrimination and prejudice.

15

Causes of obesity remain unclear, however whether obesity is of genetic origin or is promoted by a genotype-environment interaction, or both, it remains true that energy intake must have exceeded metabolic and physical (work) energy expenditure for there to have been surplus energy available for fat deposition. There remains considerable uncertainty, however, over the relative importance of different mechanisms in achieving this positive energy balance.

20

Treatment of obesity remains a problem. Although it is well established that morbidity and mortality are increased in obese individuals, it is unclear whether dieting results in decreased long-term risk of early death. The major obesity intervention has been the many different forms of dieting, which are often fads without a sound scientific basis. Results have shown that dieting is a component of the weight loss regimens of 84% of women and 76-78% of men attempting to lose weight. A further important obesity intervention is physical activity which increases energy expenditure, both during the actual period of exercise and during subsequent period of rest. Thus, exercise can promote negative energy balance provided that energy intake is not increased concomitantly. Exercise, however, in general, has been found to be only moderately successful in promoting weight loss. A program combining both

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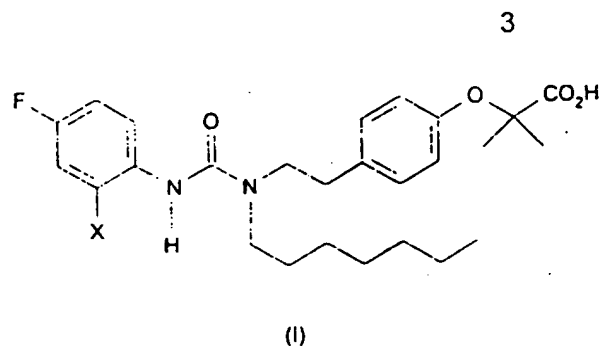
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5 dieting and exercise as well as behaviour modification is widely viewed as the optimal approach to weight loss. Food restriction alone can be very successful in promoting weight loss, but, a significant component of the weight loss can be lean tissue. In addition, food restriction results in a decline in total energy expenditure which serves to reduce the extent of negative energy balance. Studies have demonstrated that combination programs involving both food restriction and exercise promote a substantial loss of fat and, at the same time, promote a maintenance of lean tissue.

10 It can be appreciated from the above that obesity remains a problem, and that no reliable treatment thereof has been established. There is therefore a need to develop medicaments and treatment regimes effective in the alleviation of obesity. We have now unexpectedly found that a certain group of compounds are particularly advantageous for use in the treatment of obesity.

15 More particularly we have found that agonists of the peroxisome proliferator activated receptor alpha (hereinafter referred to as PPAR α) are useful in the treatment of obesity. Peroxisome proliferator activated receptor (hereinafter referred to as PPAR) is a known member of the steroid/retinoid/thyroid hormone receptor family of ligand activated transcription factors and is activated, inter-
20 alia, by high micromolar concentrations of certain peroxisome proliferators. PPAR α , peroxisome proliferator activated receptor gamma (hereinafter referred to as PPAR γ) and peroxisome proliferator activated receptor delta (hereinafter referred to as PPAR δ or NUC1) have respectively been identified as subtypes of
25 PPARs.

The present invention therefore provides PPAR α agonists for use in the treatment of obesity, and methods of treating obesity employing PPAR α agonists. More particularly, the present invention provides the use of potent and selective PPAR α agonists for use in the treatment of obesity. For example, we
30 have found that a potent and selective PPAR α agonist represented by formula (I) (or a pharmaceutically acceptable salt thereof) is useful in the treatment of obesity:



wherein X represents hydrogen or fluorine.

5

A compound of formula (I) wherein X represents fluorine is specifically disclosed in Example 3 of WO92/10468. However, there is no disclosure or suggestion in WO92/10468 of obesity treatment.

10

Reference to a compound of formula (I) as used herein includes reference to pharmaceutically acceptable salts thereof, a particularly apt salt being N-methyl-glucamine.

15

References hereinafter to a compound of formula (I) includes the compound and its pharmaceutically acceptable salts.

The following are particular aspects of the present invention:

20

(a) a PPAR α agonist (e.g. a compound of formula (I)) for use as a therapeutic agent in the treatment of obesity;

25

(b) pharmaceutical formulations comprising a PPAR α agonist (e.g. a compound of formula (I)) and at least one pharmaceutical carrier, wherein the PPAR α agonist is present in an amount effective for use in the treatment of obesity;

(c) the use of a PPAR α agonist (e.g. a compound of formula (I)) in the manufacture of a medicament for the treatment of obesity;

- (d) a method of treating obesity in a mammal, such as a human, which comprises the administration of a therapeutically effective amount of a PPAR α agonist (e.g. a compound of formula (I)) to a said mammal.

5 The term 'treatment' as used herein includes prophylaxis as well as alleviation of established obesity. In addition to the treatment of obesity, a method according to the present invention has application in the treatment of conditions associated with obesity, such as coronary heart disease, stroke, obstructive
10 sleep apnoea, diabetes mellitus, gout, hyperlipidemia, osteoarthritis, reduced fertility, impaired psychosocial function, reduced physical agility and increased risk of accidents, impaired obstetrical performance, reduced economic performance and discrimination and prejudice as herein before described.

15 A recognised clinical and epidemiological measure for the classification of obesity is the Body Mass Index (BMI) which is defined as weight in kilograms divided by the square of height in meters. Typically, a BMI of 25-30 is considered as overweight and >30 as obese. Treatment according to the present invention generally refers to a lowering of BMI to less than about 29 to 31. It will however be appreciated by persons skilled in the art that obesity is
20 inherently difficult to classify, and that the cut-off point for the definition of obesity is necessarily arbitrary, in part because body fatness is a continuum. However, in general terms treatment according to the present invention desirably prevents or alleviates obesity to an extent whereby there is no longer a significant health risk to the patient.

25 The amount of a PPAR α agonist which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the mode of administration and the precise clinical condition of the recipient. In general, the daily dose will be in the range of 0.1mg - 1g/kg, typically 0.1 -
30 100mg/kg. An intravenous dose may, for example, be in the range of 0.01mg to 0.1g/kg, typically 0.01mg to 10mg/kg, which may conveniently be administered as an infusion of from 0.1 μ g to 1mg, per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.01 μ g to 0.1mg, per millilitre. Unit doses may contain, for example, from 0.01 μ g to 1g of a PPAR α agonist. Thus
35 ampoules for injection may contain, for example, from 0.01 μ g to 0.1g and orally

administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.1mg to 1g.

5 A PPAR α agonist may be employed in the treatment of obesity as the compound per se, but is preferably presented with an acceptable carrier in the form of a pharmaceutical formulation. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the agonist as a unit-
10 dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the agonist.

The formulations include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or
15 intravenous) administration.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges or tablets, each containing a predetermined amount of a PPAR α agonist; as a powder or granules; as a
20 solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. In general, the formulations are prepared by uniformly and intimately admixing the active PPAR α agonist with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or moulding a powder
25 or granules of the PPAR α agonist optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a
30 suitable machine, the powdered compound moistened with an inert liquid diluent.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a PPAR α agonist in a flavoured base, usually sucrose and acacia or

tragacanth, and pastilles comprising the agonist in an inert base such as gelatin and glycerin or sucrose and acacia.

5 Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of a PPAR α agonist, preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the agonist with
10 water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the agonist.

15 Formulations suitable for rectal administration are preferably presented as unit-dose suppositories. These may be prepared by admixing a PPAR α agonist with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

20 Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The PPAR α agonist is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

25 A compound of formula (I) may be prepared as described in Example 3 of WO92/10468.

30 The present invention will now be further illustrated by the accompanying Examples which do not limit the scope of the invention in any way.

Example 1

35 2-(4-[2-(3-[4-fluorophenyl]-1-heptylureido)ethyl]-phenoxy)-2-methylpropionic acid (Compound of formula (I), where X = H)

1.6g of 4-fluorophenyl isocyanate was added to a solution of 3.3g of ethyl 2-[4-(heptylaminoethyl)phenoxy]-2-methylpropionate [WO 92/10468, example 2, intermediate (d)] in 50 mL of CH₂Cl₂. The resulting solution was stirred at room temperature for 18 hours and then concentrated *in vacuo*. The residue was purified by flash chromatography (SiO₂, 2:1:1 hexane/CH₂Cl₂/ethyl acetate) to yield 4.8 g of ethyl 2-(4-[2-[3-(4-fluorophenyl)-1-heptylureido]ethyl]phenoxy)-2-methylpropionate as a light brown oil.

2.4 g of ethyl 2-(4-[2-[3-(4-fluorophenyl)-1-heptylureido]ethyl]phenoxy)-2-methylpropionate was dissolved in 50 mL of ethanol and 30 mL of 1N aqueous sodium hydroxide was added. The resulting solution was heated at reflux for 30 minutes, cooled to room temperature, acidified with 100 ml of 2N aqueous HCl and extracted with CH₂Cl₂. The organic extract was washed with water and brine, dried over magnesium sulfate and concentrated *in vacuo*. The resulting solid was recrystallized from diethyl ether/hexane to yield 1.1g of the title compound as a white powder; m.p. 162-4 °C; ¹H NMR (CD₃OD, δ, 300 MHz): 7.35-6.7 (7H, m, aromatic), 3.48 (2H, t, NCH₂), 3.24 (2H, t, NCH₂), 2.76 (2H, t, ArCH₂), 1.5-1.1 (10H, m, (CH₂)₅CH₃), 1.45 (6H, s, (CH₃)₂C), 0.83 (3H, t, (CH₂)₅CH₃).

20

Example 2

Radioligand [³H]-2-(4-[2-(3-[4-fluorophenyl]-1-heptylureido)-ethyl]phenoxy)-2-methylpropionic acid

1.2 g of ethyl 2-[4-(2-aminoethyl)phenoxy]-2-methylpropionate [WO 92/10468, example 2, intermediate (c)] was dissolved in THF (20 mL). Hept-6-enal (0.43 g) and 4A sieves (0.6g) were added. After 10 minutes, 0.25 g of sodium cyanoborohydride was added and the mixture stirred at room temperature for 50 minutes. The reaction mixture was poured into 5 % aq. sodium carbonate and extracted with ethyl acetate. The organic extract was washed with brine, dried over MgSO₄ and concentrated. Purification by flash chromatography (5-10% MeOH/CH₂Cl₂) gave 0.15 g of ethyl 2-[4-(2-amino-[6-heptenyl]ethyl)phenoxy]-2-methylpropionate as a light brown viscous oil. This material was dissolved in CH₂Cl₂ (5 mL) and 4-fluorophenylisocyanate (0.05 mL) was added. The solution was stirred at rt for 3 hours and then concentrated. Purification by flash chromatography gave 0.08 g of ethyl 2-(4-[2-(3-[4-fluorophenyl]-1-[6-

heptenyl]ureido)ethyl]phenoxy)-2-methylpropionate as a yellow solid. This material was dissolved in EtOH (3 mL) and 1M aq. NaOH (1.5 mL), and the solution was heated at reflux for 30 min. The solution was concentrated, poured into 1N HCl and extracted with EtOAc, washed with brine, dried over MgSO₄,
5 and concentrated to a yellow solid. Recrystallization from ether/hexane gave 0.05g of 2-(4-[2-(3-[4-fluorophenyl]-1-[6-heptenyl]ureido)ethyl]phenoxy)-2-methylpropionic acid as a white powder; m.p. 143-5 degC.

A solution of 2-(4-[2-(3-[4-fluorophenyl]-1-[6-heptenyl]ureido)ethyl]phenoxy)-2-methylpropionic acid (10 mg) in anhydrous DMF (3.5 mL) was transferred to a
10 reaction vessel containing 10 % Pd/C (9.8 mg). The reaction vessel was evacuated and degassed via one freeze-thaw-evacuation cycle and then exposed to tritium gas (10.1 Ci). The reaction was terminated after 4.3 hours and the catalyst was removed by filtration through a short column of celite. The
15 catalyst was further washed with ethyl acetate (3 mL) and methanol (2 mL). The solvents were removed in vacuo and any labile tritium was removed by evaporation with methanol (4 x 1mL) The residue was dissolved in acetonitrile (20 mL) and filtered to provide a solution of the labeled compound (33.3 mCi/mL, 1863 mCi). HPLC analysis (Dynamax C8, 20 min gradient from 4:6
20 ACN:0.1% TFA to 9:1 ACN:0.1%TFA, 254 nm, on-line radioactivity detection with Berthold flow monitor, retention time, 22.4 min) of the solution indicated a radiochemical purity of 80%. A portion of this solution (0.8 mL, 26.6 mCi) was purified by HPLC (Dynamax C8, 25 min gradient from 4:1
AcN:0.1%TFA to 9:1 ACN: 0.1% TFA, 235 nm). Fractions containing pure
25 material were combined and evaporated under nitrogen. The residue was redissolved in acetonitrile to provide a solution of the title compound (9.38 mCi, 1.817 mCi/mL, specific activity, 83.8 Ci/mmol, radiochemical purity, 98.9%).

Example 3

30

Binding data

a) Binding of the radioligand of Example 2 to PPAR α

The ligand binding domains of mouse and human PPAR α were expressed in E. Coli as fusion proteins with glutathione-S-transferase (GST). DNA encoding the
35 ligand binding domain of mouse and human PPAR α was amplified via

polymerase chain reaction and inserted in-frame into the bacterial expression vector pGEX-2T (Pharmacia). GST-mPPAR α and GST-hPPAR α fusion proteins were expressed in BL21(DE3)plysS cells. After a 2 hour induction with 1 mM IPTG, the cells were lysed by freeze/thaw in 1/10 volumes of a buffer containing
5 50 mM Tris (pH 8), 250 mM KCl, 10 mM DTT, 1 mM PMSF, and 1% Triton X-100. Lysates were clarified by centrifugation for 1 hr at 50,000 x g. 1.5 ml of a 50% glutathione-sepharose bead (Pharmacia)/phosphate buffered saline slurry was added to 10 ml of clarified lysate, the mixture incubated for 30 minutes, and the glutathione-sepharose bead-GST-PPAR α complexes were then collected by
10 centrifugation and washed twice in binding buffer containing 50 mM KCl, 10 mM Tris (pH 8), 1 mM DTT. The washed glutathione-sepharose bead-PPAR α complexes were resuspended in 0.75 ml binding buffer containing 10% glycerol.

For binding reactions, 10-20 microliter of the glutathione-sepharose bead-PPAR α slurry was incubated at 4 degrees celsius for 2 hours in binding buffer
15 (final volume = 100 microliter) with the radioligand of Example 2 in the presence or absence of a 100-fold excess of the title compound of Example 1 (hereinafter referred to as Compound A). The glutathione-sepharose bead-GST-PPAR α complexes were collected by centrifugation and washed twice in binding buffer.
20 The glutathione-sepharose bead-GST-PPAR α complexes were then resuspended in scintillation fluid and the tritium quantitated by liquid scintillation counting.

Binding affinity analyses were done by varying the concentration of the
25 radioligand of Example 2 from 7.5 nM to 200 nM. Specific, saturable binding of Compound A was observed in experiments in which either the mouse or human PPAR α -GST fusion protein was used, K_d = 100 nM.

b) Competition binding of the Compound A, and 2-(4-[2-(3-[2,4-difluorophenyl]-1-heptylureido)ethyl]-phenoxy)-2-methylpropionic acid (Compound of formula (I),
30 where X = F, hereinafter referred to as Compound B) for PPAR α

For competition binding reactions, 10-20 microliter of the glutathione-sepharose bead-PPAR α slurry was incubated at 4 degrees celsius for 2 hours in binding buffer (final volume = 100 microliter) with 100 nM of the radioligand of Example
35 2 in the presence or absence of a 1000-fold excess (100 microM) of Compound

A or Compound B. The glutathione-sepharose bead-GST-PPAR α complexes were collected by centrifugation and washed twice in binding buffer. The glutathione-sepharose bead-GST-PPAR α complexes were then resuspended in scintillation fluid and the tritium quantitated by liquid scintillation counting.

5	No competitor	40,200 cpm bound
	Compound A	18,300 cpm bound
	Compound B	13,000 cpm bound

Example 4

10

A transient cotransfection assay was used to screen for PPAR α activator activity of compounds of formula (I).

As mammalian cell lines contain endogenous nuclear receptors that can complicate interpretation of the results, we used an established chimera system in which the ligand-binding domain of the PPAR- α was fused to the DNA binding domain of the yeast transcription factor GAL4. The GAL4-PPAR α chimera was cotransfected into CV-1 cells with a reporter construct containing five copies of the GAL4 binding site upstream of the thymidine kinase promoter driving secreted placental alkaline phosphatase (SPAP) as reporter.

20

Plasmids

GAL4-PPAR chimera and UAS-tk-CAT/SPAP reporters. The GAL4-PPAR expression constructs contain the translation initiation sequence and amino acids 1-76 of the human glucocorticoid receptor fused to a nucleotide sequence encoding for amino acids 1-147 of GAL4 in the pSG5 expression vector (Stratagene). A nucleotide sequence encoding for amino acids 174-475 of PPAR α , as amplified by polymerase chain reaction (PCR) using vent polymerase (New England Biolabs) and inserted C-terminal to the GAL4 sequences. The UAS-tk-CAT/SPAP reporter contains 5 copies of the GAL4 binding site inserted into pBLCAT2 or pG12-tk-SPAP (Luckow, B et al, 1987 and Berger et al, 1988)

25

pSG-PPAR. Nucleotide sequences encoding for PPAR α were inserted into the expression vector pSG5 (Stratagene).

30

aP2-tk-CAT. The 518 bp EcoR1/Xba1 fragment containing the enhancer of the aP2 gene (Graves et al., 1992) was inserted into pBLCAT2 (Luckow and Schutz, 1987).

5 Transfection assay: SPAP reporter. CV-1 cells were plated in DME medium supplemented with 10% delipidated fetal calf serum at a density of 2.4×10^4 cells per well in a 96-well plate (Costar) 16-24h before transfection. In general, 8.0 ng of reporter plasmid, 25.0 ng of β -galactosidase expression vector (pCH110, Pharmacia), and 2.0 ng of GAL4-PPAR α expression vector were
10 mixed with carrier DNA (pBluescript, Stratagene) to a total of 80 ng of DNA per well in a volume of 10 μ l optiME medium (GIBCO BRL). To this, a second mix, containing 9.3 μ l optiME medium (GIBCO BRL) and 0.7 μ l of LIPOFECTAMINE™ (GIBCO BRL), was added. After 30 min, an additional 80 μ l of optiME medium were added and the combined mix was then applied to the
15 cells. 16 h later the medium was exchanged to DME medium supplemented with 10% delipidated fetal calf serum and the test compound at a concentration of 10^{-5} M. After incubation for an additional 24 h SPAP activity and β -galactosidase activity were measured as previously described (Pfahl et al., 1990).

20 Transfection assay: CAT reporter. CV-1 cells were plated in DME medium supplemented with 10% delipidated fetal calf serum at a density of 1.2×10^5 cells per well in a 24-well plate (Costar) 16-24 h before transfection. In general, 100 ng of reporter plasmid, 200 ng of β -galactosidase expression vector (pCH110
25 Pharmacia), and variable amounts of receptor expression vector were mixed with carrier DNA (pBluescript, Stratagene) to 500 ng of total DNA per well in a volume of 50 μ l optiME medium (GIBCO BRL). To this mix, 50 μ l of a 1:10 dilution of LIPOFECTAMINE™ (GIBCO BRL) in optiME medium was added. After 30 min an additional 400 μ l of optiME medium was added and the total mix
30 applied to the cells. 16 h later, the medium was exchanged to DME medium supplemented with 10% delipidated fetal calf serum and the test compound at the indicated concentration. After incubation for an additional 24 h, chloramphenicol acetyl transferase (CAT) activity and β -galactosidase activity were measured as previously described (Pfahl et al., 1990). CAT activity was

normalized for transfection efficiency by using the cotransfected β -galactosidase expression plasmid (pCH110, Pharmacia) as internal standard.

The following EC₅₀ values were obtained for compounds of formula (I) employing the transfection assay.

Formula (I)	mPPAR α EC ₅₀ (nM)	hPPAR α EC ₅₀ (nM)
X = Fluorine	25	720
X = Hydrogen	13	545

Example 5

Male Golden Syrian hamsters (supplied by Charles River), weighing approximately 140-150 g at the start of the study, were subjected to the following dietary regime. On day 0, four groups of animals (n=6/group) were begun on a diet consisting of rodent chow containing 1% cholesterol. Three of the four groups on the cholesterol diet also began oral dosing with Compound A as described in Example 3 (0.05, 0.1, 0.25 and 0.5 mg/kg/day). Compound A was given as a suspension in 5% bicarbonate and 0.5% methylcellulose. The study was carried out for 14 days.

The above dietary regime was also carried out with Compound B, but the dosages of Compound B employed were 0.1, 0.5 and 1mg/kg/day.

The changes of body weight observed were as follows:

Compound A test

1. Chow containing 1% cholesterol - gained 23.2g
2. Chow containing 1% cholesterol, plus 0.05 mg/kg of Compound A - gained 20g.
3. Chow containing 1% cholesterol, plus 0.1mg/kg of Compound A - gained 26.2g.
4. Chow containing 1% cholesterol, plus 0.25mg/kg of Compound A - gained 12.6g.

5. Chow containing 1% cholesterol, plus 0.5mg/kg of Compound A - gained 3.4g.

Compound B test

- 5
1. Chow containing 1% cholesterol - gained 13g;
 2. Chow containing 1% cholesterol, plus 0.1mg/kg of Compound B - gained 11g;
 3. Chow containing 1% cholesterol, plus 0.5mg/kg of Compound B - lost 12.3g;
 4. Chow containing 1% cholesterol, plus 1mg/kg of Compound B - lost 12.4g.

CLAIMS

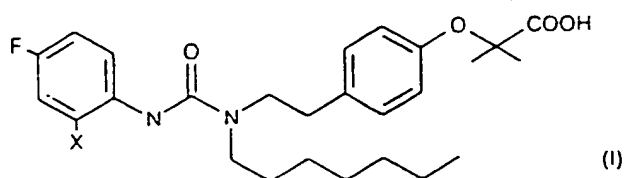
1. Use of PPAR α agonist for the manufacture of a medicament for the treatment of obesity.

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2. Use according to claim 1 wherein the PPAR α agonist is selective for PPAR α .

3. Use according to claim 2 wherein the PPAR α agonist is a compound of formula (I)

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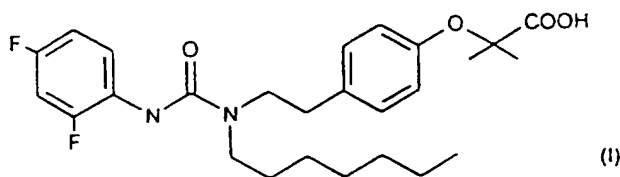


wherein X is H or F

15

or a pharmaceutically acceptable salt thereof.

4. Use according to claim 3 wherein the compound of formula (I) is



20

or a pharmaceutically acceptable salt thereof.

5. Use according to any preceding claim wherein the medicament is formulated in unit doses.

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